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LETTERS TO THE EDITOR

Hereditary angioedema: the plasma contact system out of control: comment

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We read with great interest the elegant review entitled 'Hereditary angioedema: the plasma contact system out of control' by De Maat *et al*. recently published in the *Journal of Thrombosis and Haemostasis*. [1]. In particular, we appreciated the section on the possible role of angiopoietins (Angs) and vascular endothelial growth factors (VEGFs) in the modulation of vascular permeability in patients with hereditary angioedema. The authors correctly mentioned our recent article in which we identified a substitution mutation in *ANGPT1* associated with hereditary angioedema [2]. In addition, at the end of the same paragraph, De Maat *et al*. discussed the possibility that the vasoactive mediator VEGF could contribute to the destabilization of vascular permeability in patients with hereditary angioedema. This hypothesis was also illustrated in Fig. 3 of the review, showing VEGF activating VEGF receptor (VEGFR) on endothelial cells [1]. In the same figure, it is shown that Ang1 activates the TIE2 receptor expressed on endothelial cells.

We would like to highlight the complexity of the interactions between different VEGFs and Angs and their receptors expressed on endothelial cells and also on certain immune cells. VEGF-A was initially discovered and named vascular permeability factor (VPF) [3]. In fact, the group of Dvorak demonstrated that ascites fluids from a variety of tumors and supernatants from several tumor cell lines contained an activity (i.e. VPF) that rapidly increased microvascular permeability. The vasodilating activity of VPF/VEGF-A is at least 50-fold more potent than that of histamine [3].

There is now compelling evidence that the VEGF family includes several isoforms such as VEGF-B, VEGF-C, VEGF-D, and placental growth factor, in addition to VEGF-A [4]. Moreover, there are several splicing isoforms of VEGF-A (121, 165, 189, and 206) that differ in their binding to matrix and specific receptors and coreceptors. For example, VEGF-A_{121} is acidic and freely diffusible, whereas VEGF-A_{165}, VEGF-A_{189} and VEGF-A_{206} are basic, and also bind to heparin and heparin proteoglycans on cellular surfaces and extracellular matrices [4]. VEGFs bind with different specificities to three mainly endothelial transmembrane receptors, i.e. VEGFR-1, VEGFR-2, and VEGFR-3 [5]. The angiogenic and permeability activities of VEGF-A are mediated by interaction with VEGFR-2, whereas the lymphangiogenic activity is promoted by binding to a VEGFR-2–VEGFR-3 heterodimer receptor.

Additional molecules, such as Ang1 and Ang2, modulate endothelial junctions through the engagement of two cell surface tyrosine kinase receptors, i.e. TIE1 and TIE2 [6]. Ang1 is expressed by perivascular cells, such as pericytes, and sustains endothelial cell survival. In contrast, Ang2, which is secreted by endothelial cells, acts autocrinally and paracrinally as a TIE2 ligand to promote angiogenesis and vascular permeability. TIE2 is primarily expressed on endothelial cells and binds both Angs, whereas TIE1 is an orphan receptor that can modulate TIE2 activity.

During recent years, it has become evident that several circulating (e.g. basophils, neutrophils, monocytes,

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and eosinophils) and tissue-resident (e.g. macrophages and mast cells) immune cells are important sources of different isoforms of VEGFs and Angs during inflammation [7–9]. More recently, we have provided the first evidence that activated human peripheral blood neutrophils can also release VEGF-$A_{165b,}$ which antagonizes the effects of VEGF-A [9]. Collectively, the above findings highlight the complexity of the VEGF–VEGFR and Ang–TIE interactions between circulating immune and endothelial cells, which may also be important in angioedema.

We would like to respectfully note that our group, for the first time, demonstrated that the levels of two different forms of VEGF (VEGF-A and VEGF-C) and Angs (Ang1 and Ang2) are increased in the plasma of asymptomatic patients with hereditary angioedema as compared with healthy controls [10]. Moreover, the levels of VEGF-A, VEGF-C and Ang2 are also increased in patients experiencing a higher number of angioedema attacks each year. The relevance of these findings is supported by the correlation of plasma levels of VEGF-A and Ang2 with those of cleaved high molecular weight kininogen, which is a precursor of bradykinin. In the same article, we hypothesized that VEGFs and Angs, along with increased release of bradykinin, can induce a state of vascular preconditioning that may change the threshold for the development of angiodema attacks [10].

We would like to emphasize the above findings, because the results of our study, which represented the first evidence that VEGFs and Angs are possibly involved in hereditary angioedema, were not discussed in the review by De Maat *et al*.

Addendum

Both authors were involved in writing the article and approved the final version to be published.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

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